EXHIBIT A: Reichert et al.

Monoclonal antibody successes in the clinic

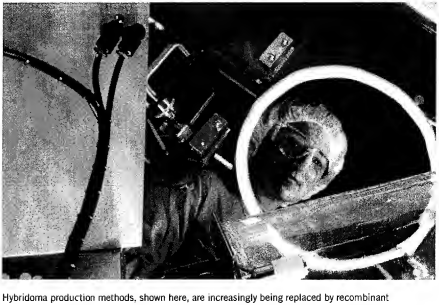
Janice M Reichert, Clark J Rosensweig, Laura B Faden & Matthew C Dewitz

Most monoclonal antibodies in clinical trials are owned by small biotech companies. But with blockbuster-sized revenues and approval rates higher than those for small-molecule drugs, that all may be set to change.

From somewhat inauspicious beginnings in the 1980s, therapeutic monoclonal antibodies (mAbs) have developed into a beneficial and profitable group of products. Monoclonal antibodies now comprise the majority of recombinant proteins currently in the clinic, with more than 150 products in studies sponsored by companies located worldwide. Starting with ideas generated in academia, biotech companies pioneered the technologies and techniques to produce therapeutic mAbs, persevered despite failures and are now being rewarded. Major pharmaceutical firms were initially reluctant to adopt the new technologies, but most now have one or more mAbs in clinical study. As a group, genetically engineered mAbs generally have higher probabilities of approval success than small-molecule drugs, and so are useful for diversification of the therapeutics pipeline.

We previously reported on trends in the development of therapeutic mAbs sponsored by US-based companies[1,2] and trends for products from all companies as of 2003 (ref. 3). Because of the dynamic nature of the clinical development process, we have continued to accumulate data (for example, initiation of clinical study of new mAbs, changes in clinical-phase status, and terminations) for these products (**Box 1**). Analysis of the current data set indicates trends toward the study of human mAbs and mAb fragments. In addition, results presented here verify our previous findings that approval success rates for chimeric and humanized mAbs are consistently in the 18–29% range.

Janice M. Reichert and Laura B. Faden are at Tufts University Center for the Study of Drug Development (CSDD), 192 South Street, Suite 550, Boston, Massachusetts 02111, USA. Clark J. Rosensweig and Matthew C. Dewitz were summer interns at CSDD.
e-mail: janice.reichert@tufts.edu



Hybridoma production methods, shown here, are increasingly being replaced by recombinant production in mammalian cells as more humanized and human mAbs enter the clinic.

Monoclonal technology evolution

The original method for production of mAbs involved fusing mouse lymphocyte and myeloma cells, yielding murine hybridomas (see **Box 2** for glossary of terms). The first report describing the preparation of hybridomas came from the UK's Medical Research Council Laboratory of Molecular Biology (Cambridge) in 1975 (ref. 4). However, the impact of the new method was not immediate[5]. The initial procedure was unreliable; as protocols were improved and materials were shared among laboratories, the technology filtered into the scientific community. Notably, the hybridoma technique was never patented (see p. 1047).

Therapeutic murine mAbs entered clinical study in the early 1980s, but problems with lack of efficacy and rapid clearance due to patients' production of human anti-mouse antibodies (HAMA) became apparent. These issues became driving forces for the evolution of mAb production technology: the potential utility of therapeutic mAbs was obvious, but the initial execution was unsatisfactory. Attempts were made to increase efficacy and decrease immunogenicity through two parallel paths: production of mAb chimeras derived from both human and mouse DNA, and production of fully human mAbs. In the case of chimeric mAbs, genetic engineering techniques were used to replace the murine Fc region with one of human sequence[6,7]. The second avenue involved applying immortalization methods and hybridoma techniques to human cells[8,9].

Surprisingly, the chimeric mAbs have proved to be superior to the early human mAbs—replacement of the murine Fc region was sufficient for improving efficacy and

Box 1 Analysis criteria

Since it was founded in 1976, Tufts CSDD has collected data on the development and approval of therapeutics and vaccines. Data for mAbs were collected by surveys of pharmaceutical and biotechnology firms, on company web sites and from public documents (such as press releases and annual reports). Commercially available databases (IDdb3, IMS R&D Focus, and PharmaProjects) were accessed to verify the status of products currently in clinical study. Products in phase 1/2 were assigned to phase 2 and products in phase 2/3 were assigned to phase 3. Data were updated with all changes noted through June 2005.

The mAb data set contained 355 therapeutic products in clinical study sponsored by more than 100 commercial firms located worldwide. Of the 355 products, 152 mAbs are currently in clinical study, with 63 in phase 1, 74 in phase 2 and 15 in phase 3. Products developed in-house or licensed from any source were included. The years in which clinical studies were initiated were not available for nine (2.5%) of the products. These products, and an additional eight mAbs that entered clinical study in 2005 as of June, were not included in the data used for

Figure 1. Bispecific and primatized mAbs, as well as products of unknown mAb type (4.5% of the data set), were excluded from probability-of-success calculations. The remaining four types of mAbs (murine, chimeric, humanized and human) comprised 90% of the data set.

Approval success calculations were based on products with a known fate (US approval or discontinuation). Percent completion was defined as the percentage of products with a known fate in a given cohort. Phase transition percentages (**Fig. 2**) were calculated as follows: the number of products that completed a given phase and entered the next was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation. Transitions occurring between phases of clinical studies conducted worldwide were included. The immunological therapeutic category includes treatments for diseases characterized by defects in the immune system that are not currently accepted as having an infectious cause (such as rheumatoid arthritis, Crohn disease or multiple sclerosis).

reducing the HAMA response for at least some products. In fact, five chimeric mAbs are now marketed in numerous countries as treatments for a variety of diseases (Table 1). The fault of the early human mAbs lay not necessarily in themselves, but in the production method. Establishment of human hybridomas and the production of sufficient amounts of human mAbs from human cell lines proved to be difficult[8,10]. Nevertheless, one human anti-endotoxin IgM mAb, nebacumab (Centoxin; Centocor, now a wholly owned subsidiary of Johnson & Johnson, New Brunswick, New Jersey) was briefly marketed for septic shock and Gram-negative bacteremia outside the United States in the early 1990s, but was withdrawn for safety reasons likely specific to the indication and mechanism of action rather than the type of mAb[11].

Box 2 Glossary of mAb terms (reprinted from ref. 1)

Antibody. Complex protein-based molecules produced by B-lymphocytes that bind to and help eliminate foreign and infectious agents in the body. Antibodies are Y-shaped, having two sets of branches attached to a single stem. The arms of the Y (Fab) are the so-called variable regions, the tips of the arms contain antigen-binding regions (complementarity-determining regions or CDRs) and the stem (Fc) is a constant region. The constant regions trigger effector functions (phagocytosis, cytolysis by cytotoxic lymphocytes or initiation of complement cascade followed by cell lysis) by linking the complex to other cells of the immune system.

Monoclonal antibody (mAb). Originally, mAbs were antibodies produced from a single B-lymphocyte. Genetic manipulation now allows genes from multiple sources of B-lymphocytes (for example, mouse and human) to be combined. mAbs of a defined peptide sequence have identical antigen-binding regions and bind to the same site (the epitope) of an antigen.

Murine (mouse) mAb. A mAb derived entirely from mice, specifically murine hybridomas generated from the fusion of mouse myeloma and mouse B-lymphocyte cells.

Chimeric mAb. A mAb constructed from variable regions derived from a murine source and constant regions derived from a human source.

Humanized mAb. A mAb constructed with only antigen-binding regions (also called complementarity-determining regions or CDRs) derived from a mouse, and the remainder of the variable regions, and constant regions, derived from a human source.

Primatized mAb. A mAb constructed from variable regions derived from cynomolgus macaques and constant regions derived from a human source. Primatized is a registered US trademark of Cambridge, Massachusetts-based Biogen Idec.

Human mAb. A mAb derived entirely from a human source, currently transgenic mice or phage display. Human mAbs can also be produced from human hybridomas or human B-lymphocyte cell lines immortalized by Epstein-Barr virus. However, these cell lines are unstable and produce only small amounts of mAbs.

Chimeras were not the only possible result of mAb genetic engineering, though. Soon after chimeric mAbs were described, work on humanized mAbs was also reported[12]. The perception of risk associated with the presence of murine protein sequence inexorably drove the technology from the murine products toward humanized ones, bypassing the chimeras, though the ultimate goal was an efficient production method for fully human mAbs. The development of phage display technology and transgenic mice in the early 1990s provided the desired methods, but realization of the goal was delayed until the end of the decade because of disputes over patents on the technologies (see p. 1079).

Advancements in genetic engineering techniques have finally provided the long-sought human mAbs, and have also opened the door to the study of varied mAb fragments, including single-chain variable fragments and antigen-binding fragments (see p. 1126). However, even mAb fragments are complex molecules, and a variety of factors must be considered (for example, specificity or avidity) before one is selected as a clinical candidate. Increased control over the design of these molecules might increase the rate of success in the future.

Table 1 US and EU therapeutic mAb approvals to date

Generic	Company/location	Trade	Description	Therapeutic category	Approval date
Muromonab-CD3	Johnson & Johnson New Brunswick, New Jersey	Orthoclone OKT3	Murine, IgG2a. anti-CD3	Immunological	06/19/86 (US)
Abciximab	Centocor	ReoPro	Chimeric, IgG1. anti-GPIIb/IIIa, Fab	Hemostasis	12/22/94 (US)
Rituximab	Genentech	Rituxan	Chimeric, IgG1κ, anti-CD20	Oncological	11/26/97 (US) 06/02/98 (EU)
Daclizumab	Hoffmann-La Roche Basel	Zenapax	Humanized, IgG1κ, anti-CD25	Immunological	12/10/97 (US) 02/26/99 (EU)
Basiliximab	Novartis Basel	Simulect	Chimeric, IgG1κ, anti-CD25	Immunological	05/12/98 (US) 10/09/98 (EU)
Palivizumab	MedImmune Gaithersburg, Maryland	Synagis	Humanized, IgG1κ, anti-respiratory syncytial virus	Anti-infective	06/19/98 (US) 08/13/99 (EU)
Infliximab	Centocor	Remicade	Chimeric, IgG1κ, anti-tumor necrosis factor (TNFα)	Immunological	08/24/98 (US) 08/13/99 (EU)
Trastuzumab	Genentech	Herceptin	Humanized, IgG1κ, anti-HER2	Oncological	09/25/98 (US) 08/28/00 (EU)
Gemtuzumab ozogamicin	Wyeth Madison, New Jersey	Mylotarg	Humanized, IgG4κ, anti-CD33; immunotoxin	Oncological	05/17/00 (US)
Alemtuzumab	Genzyme Cambridge, Massachusetts	Campath-1H	Humanized, IgG1κ, anti-CD52	Oncological	05/07/01 (US) 07/06/01 (EU)
Ibritumomab tiuxetan	Biogen Idec	Zevalin	Murine, IgG1κ, anti-CD20; radiolabeled (Yttrium 90)	Oncological	02/19/02 (US) 01/16/04 (EU)
Adalimumab	Abbott Deerfield Park, Illinois	Humira	Human, IgG1κ, anti-TNFα	Immunological	12/31/02 (US) 09/1/03 (EU)
Omalizumab	Genentech	Xolair	Humanized, IgG1κ, anti-IgE	Immunological	06/20/03 (US)
Tositumomab-I131	Corixa Seattle	Bexxar	Murine, IgG2aλ, anti-CD20; radiolabeled (Iodine 131)	Oncological	06/27/03 (US)
Efalizumab	Genentech	Raptiva	Humanized, IgG1κ, anti-CD11a	Immunological	10/27/03 (US) 09/20/04 (EU)
Cetuximab	Imclone Systems New York	Erbitux	Chimeric, IgG1κ, anti-Epidermal growth factor receptor	Oncological	02/12/04 (US) 06/29/04 (EU)
Bevacizumab	Genentech	Avastin	Humanized, IgG1, anti-vascular endothelial growth factor	Oncological	02/26/04 (US) 01/12/05 (EU)
Natalizumab[a]	Biogen Idec	Tysabri	Humanized, IgG4κ, anti-α4-integrin	Immunological	11/23/04 (US)

See **Box 1** for methodology.
[a]Voluntary suspension of natalizumab marketing announced February 28, 2005.

Entering the clinic

The therapeutic potential of mAbs was recognized early on, but the number of products ready for clinical study was limited in the early 1980s (Fig. 1). A surge in the clinical initiations of mAb products started in 1984, but reached a local maximum in 1987. Most of the products (89%) entering clinical study between 1980 and 1987 were murine mAbs that ultimately failed in the clinic. Clinical development of murine products declined dramatically between 1987 and the mid-1990s, then gradually dropped to zero in 2003.

A plateau in clinical initiations occurred while less immunogenic mAbs were developed. Starting in 1992, the loss of the murine mAbs was offset by a rise in the number of humanized products entering clinical study. Of the four types—murine, chimeric, humanized and human—human mAbs constituted the largest number entering clinical study per year by 2001. In contrast, the number of chimeric mAbs entering clinical study per year has been consistently low since the mid-1980s, when these products first began to enter clinical trials.

Moving through the phases

We calculated probabilities for making transitions between clinical phases for the chimeric and humanized mAbs in the data set (Fig. 2). Results for human mAbs were not included because most of these products are still in clinical study, and therefore few have known fates. The probability of transition from US Food and Drug Administration (FDA) review to approval was 100% for the cohorts presented, so results for the transition from phase 3 to regulatory review were combined with those for transition from review to approval. For any cohort, the arithmetic product of the phase transitions exactly equals the overall approval success rate only when the fates of all products are known (that is, when the percent completion is 100%). Thus, calculated results should be considered estimates when the percent completion is below 100%.

Overall, the chimeric mAbs tended to have lower probabilities of transitions from phases 1 to 2 and phases 2 to 3 than the humanized products. However, the probability of receiving FDA approval once the product was in phase 3

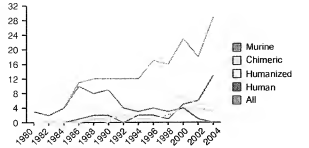


Figure 1 Number of therapeutic mAbs entering clinical study per year (1980–2004). Data are presented as two-year moving averages.

was higher—actually 100%—for the chimeric mAbs. Taken together, these results suggest that stringent selection criteria for advancement were applied to the chimeric clinical candidates after phases 1 and 2, thus ensuring that only successful products entered critical, and expensive, phase 3 studies. It should be noted that several of the chimeric mAb cohorts included only a small number of products.

Approval success

The FDA has approved a total of 18 therapeutic mAbs (**Table 1**), although one, natalizumab (Tysabri; Biogen Idec, Cambridge, Massachusetts) has since been voluntarily withdrawn. Most of the approvals have come in the past decade; only two products (11%) were approved before 1997. Most mAbs have been studied as treatments for either oncological or immunological indications. FDA-approved mAbs in these two therapeutic categories comprise 89% of the total. The chimeric and humanized products comprise 14 (78%) of the approved mAbs, and one human mAb, adalimumab (Humira; Abbott), was approved in 2002.

Only three (17%) approved mAbs are murine products. The first mAb approved, muromonab-CD3 (Orthoclone; Johnson & Johnson) was a murine anti-CD3 product used as a treatment to reverse transplant rejection in immunosuppressed patients. More recently, two radiolabeled murine mAbs, ibritumomab tiuxetan (Zevalin; Biogen Idec) and tositumomab-I-131 (Bexxar; Corixa, Seattle, Washington, now a wholly owned subsidiary of GlaxoSmithKline, Brentford, UK), were approved for non-Hodgkin lymphoma. The potency of a radiolabel allows administration of very small amounts of these products, so immunogenicity from the murine protein is less of a concern. Because of their limited utility, however, clinical study of most of the murine mAbs has been discontinued. Overall, the approval success rate calculated for murine products was 3%. Few murine mAbs remain in clinical study; the success rate for the group would not dramatically improve, even if some were to be approved.

In contrast to the murine products, the chimeric and humanized mAbs have been much more successful—these products comprise 28% and 50%, respectively, of FDA-approved mAbs. Approval success rates for the chimeric and humanized mAb therapeutics included in the data set were 21% and 18%, respectively (**Table 2**). Only slight variations in the success rates were observed when the products were stratified by therapeutic category. Chimeric mAbs for immunological indications had a somewhat higher approval success rate compared with the oncology products (22% versus 18%, respectively), but this order was reversed for the humanized products (19% versus 24%, respectively).

Success rates were also calculated for products that entered clinical study before 1998. The periods selected correspond to the intervals between the year clinical study was initiated for the first of each mAb type through 1998. On average, the clinical development phase for the FDA-approved therapeutic mAbs is 6.5 years. Thus, a reasonable amount of time has passed (a minimum of 7.5 years from 1998 to mid-2005) for determination of the fates of the products. Approval success rates for the chimeric and humanized mAb therapeutics stratified by time were 29% and 25%, respectively. These values represent the most accurate overall approval success rates for chimeric and humanized mAbs we have calculated to date. It remains to be seen whether the success rates will be the same for mAbs currently in the clinical pipeline. Again, it should be noted that the chimeric mAb cohorts are much smaller when compared with similar groups of humanized mAbs.

The Tufts University Center for the Study of Drug Development (CSDD) reported approval success rates for therapeutic mAbs sponsored by only US-based companies in 2001 (ref. 1). The chimeric and humanized mAbs from the US-focused data set had approval success rates of 24% and 25%, respectively. The current data set includes approximately twice the total number of products (353 versus 186 mAbs) and nearly twice the number of approved products (18 versus 10 mAbs) compared with the data set analyzed in the 2001 study. The success rates reported here for chimeric and humanized mAbs (21% and 18%, respectively) are slightly lower, but this is not surprising because 'success' was defined here as FDA approval only, although products from companies located worldwide were included in the data set.

Several therapeutic mAbs have been approved only outside the US. One murine mAb, edrecolomab (Panorex; Centocor), and one human mAb, nebacumab (Centoxin; Centocor), were approved in the 1990s for treatment of colorectal cancer and septic shock/Gram-negative bacteremia, respectively. However, the products were subsequently withdrawn from their non-US markets. In addition, three therapeutic mAbs were recently approved in Asia. China's State Drug Administration (Beijing) has approved two oncology mAbs: in 2003, a chimeric, I^{131}-radiolabeled mAb that targets histone H1–DNA complexes in necrotizing tumor cells from MediPharm Biotech (Shanghai, China); and in 2005, nimotuzumab, a humanized mAb from YM Bioscience (Mississauga, Ontario, Canada). Japan's Ministry of Health, Labor and Welfare approved tocilizumab, a humanized anti-interleukin 6 receptor mAb from Chugai (Tokyo) as a treatment for Castleman disease in 2005.

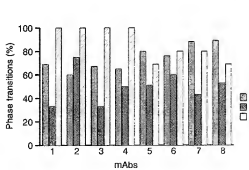


Figure 2 Clinical phase transition percentages for therapeutic mAbs, according to FDA data. (See **Box 1** for methodology.) 1, chimeric mAbs, all products ($n = 39$); 2, oncological chimeric mAbs ($n = 21$). 3, immunological chimeric mAbs ($n = 9$). 4, chimeric mAbs, 1987–1997 ($n = 20$). 5, humanized mAbs, all products ($n = 102$), 6, oncological humanized mAbs ($n = 46$). 7, immunological humanized mAbs ($n = 34$); 8, humanized mAbs, 1988–1997 ($n = 46$). See **Table 2** for completion rates for these.

Table 2 Approval success rates for mAbs

mAb type and area of application[a]	Total number of mAbs	Number discontinued	Number FDA approved	Completion[b] (%)	Approval success[c] (%)
Chimeric mAbs, all products	39	19	5	62	21
Oncological chimeric mAbs	21	9	2	52	18
Immunological chimeric mAbs	9	7	2	100	22
Chimeric mAbs, 1987–1997	20	12	5	85	29
Humanized mAbs, all products	102	41	9	49	18
Oncological humanized mAbs	46	13	4	37	24
Immunological humanized mAbs	34	17	4	62	19
Humanized mAbs, 1988–1997	46	24	9	72	27

[a]See Box 1 for inclusion criteria. [b]Percent completion, percentage of products with a known fate in a given cohort. [c]Phase 1 to approval in the United States.

Upcoming monoclonals

The current pipeline of therapeutic mAbs in clinical study contains more than 150 products. Of the total in the clinic, 63 (41%) are in phase 1. This group of products is the least well defined of the data set because often only limited information is available at this early stage of the process. For example, of the entire data set, mAb type is unknown for only 4.5%, but two-thirds of these are found in phase 1. Taking into account the uncertainty in the data, we can say that humanized and human mAbs comprise a minimum of 24% and 43%, respectively, of the products in phase 1. In contrast, humanized products constitute the greatest portion of the mAbs in phase 2 and phase 3 (39% and 47%, respectively), though the human mAbs run a close second (comprising 31% and 33% of those in phase 2 and phase 3, respectively).

Most therapeutic mAbs are studied as treatments for diseases in only three therapeutic categories: oncological, immunological and anti-infective (**Fig. 3**). The relative proportion of each category has even remained fairly consistent. One notable exception is the reduction in the number of immunological mAbs in phase 1. This decrease likely is due to competition from the approved immunological mAb products.

The group of products in phase 3 (**Table 3**) highlights the trend toward the study of fragments, rather than full-size mAbs. Only one FDA-approved product, abciximab (ReoPro; Centocor), is a mAb fragment. In contrast, seven of the mAbs currently in phase 3 are variations on the mAb theme. Some targets are inaccessible to full-sized mAbs, so decreasing size while maintaining functionality and specificity might increase the potential utility of the products.

Where to from here?

Therapeutic mAbs, and the technology to produce them, have evolved over the past quarter century and will continue to do so in the future. Products derived from early technology have mostly fallen by the wayside, though some chimeras are still in active development. Small biotech companies sponsor the majority of chimeric mAbs now in clinical study. The chimeric products might be attractive for several reasons: use of the older technology may allow firms to avoid technology licensing or royalty fees levied for production of humanized and human mAbs, and, despite the purported risk of HAMA, careful selection of chimeric clinical candidates can yield blockbusters. For example, several chimeric mAbs are truly billion dollar molecules—infliximab (Remicade; Centocor) and rituximab (Rituxan; Genentech, S. San Francisco, California) each had over $2 billion in global sales during 2004.

Still, a trend toward clinical study of human products is clear. This result follows from the attempts to reduce mAb immunogenicity by reducing the quantity of murine sequence in the products. Even so, the immunogenicity problem does not disappear with the murine component. The human immune system can potentially produce antibodies to any protein therapeutic. Labels for most of the FDA-approved mAbs report that at least some patients developed detectable antibodies to the products. The labels also note that the identification of anti-mAb antibodies is highly dependent on the sensitivity and specificity of the assay, thus making comparisons between immunogenicity rates difficult. Nevertheless, on the basis of labeling information, three each of the humanized and chimeric mAbs, and the one human mAb, have immunogenicity rates in the range of 5–10%. Immunogenicity is not a fatal flaw now, but rather a problem that can be managed.

Therapeutic mAbs are now big business. Six FDA-approved products each had global sales over $500 million in 2004. This income helps keep firms in business and spurs mAb development at other firms. Analysis of the average wholesale price[13], dosing information and indications suggests that FDA-approved mAbs are differentially priced by therapeutic category. Oncology mAbs, with smaller markets, are priced much higher than mAbs for immunological diseases that tend to have larger markets (for example, rheumatoid arthritis, Crohn disease, psoriasis and asthma). The cost of protein therapeutics to the US health care system, which is already considered overburdened, has raised the question of approval for biosimilars (generic versions of biologics, also known as follow-on biologics). However, three factors suggest mAb biosimilars will not be seen any time soon: the complexity of mAb production, current lack of a regulatory pathway to approval and patent protection covering all the recently approved products.

According to our analysis of the therapeutic protein pipeline, study of human mAbs and of mAb fragments is the wave of the future. On

Figure 3 Therapeutic categories for mAbs in clinical study. Misc., miscellaneous category including ophthalmic, neuropharmacologic and cardiovascular indications.

Table 3 Therapeutic mAbs currently in phase 3 studies

Company/location	Generic/code name	Brand name	Description
Abgenix Fremont, California	Panitumumab		Human, IgG2κ, anti-EGF receptor
Amgen Thousand Oaks, California	AMG-162		Human, IgG2, anti-RANKL
Genmab Copenhagen	Zanolimumab	Humax-CD4	Human, IgG, anti-CD4 receptor
Medarex Princeton, New Jersey	MDX-010		Human, IgG1κ, anti-CTLA 4
Neutec Manchester, UK	Anti-MRSA mAb	Aurograb	Human, anti-MRSA; single chain
Alexion Pharmaceuticals Cheshire, Connecticut	Pexelizumab		Humanized, anti-complement C5; single-chain variable fragment
Alexion Pharmaceuticals	Eculizumab		Humanized, IgG, anti-C5; single chain
Genentech	Ranibizumab	Lucentis	Humanized, IgG1, anti-VEGF; Fab fragment
GlaxoSmithKline	Mepolizumab		Humanized, IgG1, anti-IL5
Immunomedics Morris Plains, New Jersey	Epratuzumab	Lymphocide	Humanized, IgG1, anti-CD22
MedImmune	Anti-RSV mAb	Numax	Humanized, anti-RSV
UCB Brussels	Certolizumab Pegol	Cimzia	Humanized, IgG, anti-TNFα, pegylated Fab' fragment
Abbott	Afelimomab	Segard	Murine, IgG3κ, anti-TNFα; $F(ab)_2$
Trion Martinsried, Germany	Catumaxomab	Removab	Bispecific, anti-CD3/EpCam; trifunctional
Wilex Munich, Germany	WX-G250	Rencarex	Chimeric, IgG1, anti-carbonic anhydrase IX

CTLA, cytotoxic T-lymphocyte associated protein; EGF, epidermal growth factor; MRSA, methicillin-resistant *Staphylococcus aureus*; RANKL, receptor for activation of nuclear factor-κ B ligand; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

the basis of the historical data set, approval success rates in the 18–29% range might be expected; success rates for the newer products will be estimates for the foreseeable future, because most of the products are still in clinical study. The overall success rates for new chemical entities (NCEs) as a whole and NCEs in oncology were recently reported to be 11% and 5%, respectively[14]. Our results[1–3] have repeatedly shown that chimeric and humanized mAbs have higher success rates than NCEs, notably in the oncology category. Results for the immunological category cannot be directly compared because of differences in the definition of the NCE and mAb cohorts. The combination of the efficient production of mAbs specifically designed to be safe and efficacious and the approval and marketing success of an increasing number of mAbs will continue to draw interest from biotech and pharmaceutical firms alike.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of the companies that provided survey data. We also thank H. Pujar for reviewing the manuscript and for providing helpful comments and suggestions.

1. Reichert, J.M. Monoclonal antibodies in the clinic. *Nat. Biotechnol.* **19**, 819–822 (2001).
2. Reichert, J.M. Therapeutic monoclonal antibodies: trends in development and approval in the US. *Curr. Opin. Mol. Ther.* **4**, 110–118 (2002).
3. Reichert, J. & Pavlou, A. Monoclonal antibodies market. *Nat. Rev. Drug Discov.* **3**, 383–384 (2004).
4. Kohler, G. & Milstein, C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* **256**, 495–497 (1975).
5. Milstein, C. The hybridoma revolution: an offshoot of basic research. *Bioessays* **21**, 966–973 (1999).
6. Morrison, S.L. *et al.* Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains. *Proc. Natl. Acad. Sci. USA* **81**, 6851–6855 (1984).
7. Boulianne, G.L. *et al.* Production of functional chimaeric mouse/human antibody. *Nature* **312**, 643–646 (1984).
8. Cole, S.P., Campling, B.G., Atlaw, T., Kozbor, D. & Roder, J.C. Human monoclonal antibodies. *Mol. Cell. Biochem.* **62**, 109–120 (1984).
9. Carson, D.A. *et al.* Human lymphocyte hybridomas and monoclonal antibodies. *Adv. Immunol.* **38**, 275–311 (1986).
10. Pasqualini, R. & Arap, W. Hybridoma-free generation of monoclonal antibodies. *Proc. Natl. Acad. Sci. USA* **101**, 257–259 (2004).
11. Inglis, T.J.J. *et al.* Monoclonal antiendotoxin agent HA-1A (Centoxin). *Lancet* **341**, 303 (1993).
12. Jones, P.T. *et al.* Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature* **321**, 522–525 (1986).
13. Fleming, T. (ed.). *Red Book* (Thomson PDR, Montvale, New Jersey, 2004).
14. Kola, I. & Landis, J. Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* **3**, 711–715 (2004).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Kiener, P. et al.

Application Number: 10/823,254

Filed: Apr 12, 2004

Group Art/ Con No.: 1642/5469

Examiner: Halvorson, M

Atty. Docket No.: EP400US

Title: EphA2 and hyperproliferative cell disorders

STATEMENT REGARDING THE PERMANENCE AND AVAILABILITY OF DEPOSITED MICROORGANISMS UNDER 37 C.F.R. 1.801-1.809

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

We, attorneys for MedImmune, Inc., having a place for the transaction of business at One MedImmune Way, Gaithersburg, Maryland 20878, the assignee of the above-captioned application, declare and state that:

1. A hybridoma expressing the anti-EphA2 antibody Eph099B-102.147 was deposited with the American Type Culture Collection (ATCC), located at 10901 University Boulevard, Manassas, Virginia 20110-2209 on August 7, 2002, in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure ("Budapest Treaty") on behalf of MedImmune, Inc. The deposited microorganism was assigned Accession No. PTA-4572.
2. A hybridoma expressing the anti-EphA2 antibody Eph099B-208.261 was deposited with the American Type Culture Collection (ATCC), located at 10901 University Boulevard, Manassas, Virginia 20110-2209 on August 7, 2002, in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure ("Budapest Treaty") on behalf of MedImmune, Inc. The deposited microorganism was assigned Accession No. PTA-4573.

3. A hybridoma expressing the anti-EphA2 antibody Eph099B-210.248 was deposited with the American Type Culture Collection (ATCC), located at 10901 University Boulevard, Manassas, Virginia 20110-2209 on August 7, 2002, in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure ("Budapest Treaty") on behalf of MedImmune, Inc. The deposited microorganism was assigned Accession No. PTA-4574.

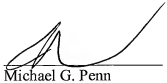
4. A hybridoma expressing the anti-EphA2 antibody B233, also known as Eph099B-233.152 was deposited with the American Type Culture Collection (ATCC), located at 10901 University Boulevard, Manassas, Virginia 20110-2209 on May 12, 2003, in compliance with the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure ("Budapest Treaty") on behalf of MedImmune, Inc. The deposited microorganism was assigned Accession No. PTA-5194.

5. We hereby assure the United States Patent and Trademark Office and the public that (a) all restrictions on the availability the public of the microorganisms referred to in paragraphs 1, 2, 3, or 4 will be irrevocably removed upon issuance of a United States patent of which such microorganisms are subject; (b) the microorganism(s) will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited microorganism(s) was received by the ATCC, and in any case, samples will be stored under agreements that would make them available beyond the enforceable life of the patent for which the deposit was made; (c) should the deposit become non-viable, it will be replaced by the assignee; and (d) access to the microorganism(s) will be available to the Commissioner during the pendency of the patent application or to one determined by the Commissioner to be entitled to such microorganism(s) under 37 C.F.R § 1.14 and 35 U.S.C. § 122. A copy of the Receipts of Deposit for the microorganisms referred to in paragraphs 1, 2, 3, and 4 have been attached to this statement as Exhibit 1 and Exhibit 2.

6. We hereby declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true and further that we make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both,

under § 1001 Title 18, and would jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,



Date: September 4, 2007

Michael G. Penn
Reg. No. 55,532
Attorney for Applicant

MEDIMMUNE, INC.
One MedImmune Way
Gaithersburg, MD 20878
Phone: (301) 398-5565
Fax: (301) 398-8565

Exhibit 1

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-365-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.

To: (Name and Address of Depositor or Attorney)

MedImmune, Inc.
Attn: Karyn Munyon
35 W. Watkins Mill Road
Gaithersburg, MD 20878

Deposited on Behalf of: MedImmune, Inc.

Identification Reference by Depositor:	Patent Deposit Designation
Mouse Hybridoma: Eph099B-102.147	PTA-4572
Mouse Hybridoma: Eph099B-208.261	PTA-4573
Mouse Hybridoma: Eph099B-210.248	PTA-4574

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received August 7, 2002 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested August 13, 2002. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Marie Harris

Marie Harris, Patent Specialist, ATCC Patent Depository

Date: August 29, 2002

cc: Marilyn Maracic
(Ref: Docket or Case No.: 10271-073-888)

Exhibit 2

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-365-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

MedImmune, Inc.
Attn: Karyn Munyon
35 West Watkins Mill Road
Gaithersburg, MD 20878

Deposited on Behalf of: MedImmune, Inc.

Identification Reference by Depositor:	Patent Deposit Designation
Mouse Hybridoma: Eph099B-233.152 anti-EphA2 CF1 CFM 06NOV02	PTA-5194

The deposit was accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposit was received May 12, 2003 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested May 20, 2003. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Marie Harris

Marie Harris, Patent Specialist, ATCC Patent Depository

Date: June 4, 2003

cc: Pennie & Edmonds LLP
Ref: Docket or Case No.: 10271-097-999